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Blistering Disorders: A Multispeciality Problem

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Abstract

Background: Blistering disorders are a heteregeneous group of disorders that can affect either skin and mucous membrane, or both, varying in presentation, clinical course, pathophysiology, immunopathology and treatment. Not infrequently the diagnosis is delayed. This can result in severe, and sometimes fatal consequences. Although these diseases are rare, it is very important to make an accurate diagnosis based on a combination of clinical profile and laboratory investigations.

Introduction

Blistering diseases are a group of severe and often therapy resistant disorders characterized by blisters and erosions on the skin and mucosa as a result of defective adhesion within the epidermis or between the epidermis and the dermis. The pathogenesis of these disorders has been extensively investigated with molecular-genetic and molecular-biological techniques in recent years and is now well understood. The underlying problem is a defect in either the dermoepidermal junction or the desmosomes. In the genetic disorders of the epidermolysis bullosa family, mutations in the structural proteins of the dermoepidermal junction impair their functions. In the acquired autoimmune bullous diseases, circulating autoantibodies bind to epidermal or junctional structures, perturb their functions, and contribute to the development of blisters. There are interesting parallels between the inherited and acquired blistering disorders because the same molecules are involved in both processes.

Blistering disorders are a heterogeneous group of disorders that can affect either skin and mucous membrane, or both, varying in presentation, clinical course, pathophysiology, immunopathology and treatment. Not infrequently the diagnosis is delayed. This can result in severe, and sometimes fatal consequences. Although these diseases are rare, it is very important to make an accurate diagnosis based on a combination of clinical profile and laboratory investigations. The identification of the specific target antigens for the autoantibodies in the autoimmune bullous diseases has led to the discovery of many components of the desmosome and the adhesion complex linking the epidermis to the dermis to be the causative factor in blistering diseases. In parallel with this work, it has been the realised that mutations of these

proteins are the basis of some of the genetic bullous diseases [**1, 2**].

These disorders have a dramatic impact on the patient and their family, and severe economic consequences for their relatives and health services. These disorders have been the subject of intensive study in recent years, and the discovery of causative genes underlying the genetic blistering disorders has increased our knowledge not only of the pathogenesis of these disorders but also of the normal biology of the skin.

Blistering diseases primarily give rise to vesicles (i.e. 5 mm or less in diameter) or bullae (i.e. over 5 mm in diameter of fluid filled lesions). Blisters are accumulation of fluid lying within or below the epidermis [**3, 4**].

Classification: The blistering disorders can be broadly divided into:

1. Genetic blistering disorders, which include *Hailey-Hailey* disease, and epidermolysis bullosa.

2. Autoimmune or immunobullous disorders, typified by pemphigus vulgaris, its subtypes and bullous pemphigoid.

3. Other causes: Porphyrias, drug reactions, mechanical, chemical and physical factors, infections, diabetes mellitus [**5, 6**].

These disorders are characterised by the formation of blisters (i.e. vesicles and bullae) on skin, and involvement of mucous membranes in the form of blisters, erosions and scarring. These disorders can be associated with multisystem involvement and various autoimmune connective diseases. These disorders, if appropriately diagnosed and treated, can lead to a significant reduction in the morbidity and mortality associated with these disorders [**7**].

History of Bullous Disorders

The Greeks used the terms pemphix, pomphos and pompholyx to describe blisters. The term pemphigus was first used by *de Sauvages* in 1760, but the bullous eruption which he described as pemphigus major probably represented erythema multiforme. *Wichmann* in 1791 gave the word pemphigus its present meaning, that of a chronic bullous disease. The term pemphigus foliaceus was coined by *Cazenave* in 1844, pemphigus vulgaris by *Ferdinand von Hebra* in 1860, dermatitis herpetiformis by *Louis Duhring* in 1884, pemphigus vegetans by *Neumann* in 1886, and epidermolysis bullosa herediteria by *Heinrich Koebner* in 1886. The *Nikolsky* sign was first described by *Nikolsky* as a characteristic sign of pemphigus foliaceus in 1895.

The diagnosis of bullous disorders can be helped by determining the age group affected, histology and pathogenesis, whether autoimmune or not, and by the morphological nature of lesions [**8, 9**].

Causes of blistering in different age groups: Age is an important guide for narrowing the diagnosis of bullous disorders, as some presentations are more predominant in different age groups. The causes in different age groups are as under:

Neonates and children: The causes in this age group are broadly classified into:

1. Infective: Herpes simplex, varicella, hand-foot-mouth disease, candidiasis, congenital syphilis, bullous impetigo, staphylococcal scalded skin syndrome etc.

2. Inflammatory: Bullous mastocytosis, erythema toxicum neonatorum, transient neonatal pustular melanosis, sucking blisters etc.

3. Genetic causes: Epidermolysis bullosa, incontinentia pigmenti, bullous congenital ichthyosiform erythretroderma etc.

4. Antibody mediated: linear IgA disease and pemphigus vulgaris.

5. Metabolic: Acrodermatitis enteropathica [**10**].

Common causes of blistering in adults: These are broadly divided into following headings:

1. Infections: Herpes simplex, herpes zoster, candidiasis etc.

2. Inflammatory: Pustular psoriasis, subcorneal pustular dermatosis.

3. Genetic: *Hailey-Hailey* disease, *Darier*'s disease.

4. Antibody mediated: Pemphigus group of diseases, paraneoplastic pemphigus, linear IgA disease, bullous pemphigoid, mucous mem-

brane pemphigoid, dermatitis herpetiformis, epidermolysis bullousa acquisita.

5. Mechanical: Frictional blisters.

6. Dermatitis: Allergic contact dermatitis, irritant dermatitis.

7. Environmental: Phototoxic reactions, photoallergic reactions, burns.

8. Drugs: Bullous drug reactions, bullous fixed drug reaction, erythema multiforme, *Stevens-Johnson* syndrome/Toxic epidermal necrolysis.

9. Metabolic: Diabetic bullae, porphyria cutanea tarda [**11, 12**].

Histopathology and pathogenesis: Histopathology reveals the location of the blister and helps to classify the type of the bullous disorder. The level of cleavage, mechanism of blister formation, and the type of inflammatory infiltrate can be determined by microscopic study. Ideally a fresh blister should be biopsied [**13**].

1. Level of cleavage in some common bullous disorders: The level of cleavage can be

A. Intraepidermal, which can be subcorneal or granular (eg; bullous impetigo, subcorneal pustular dermatosis, staphylococcal scalded skin syndrome)

B. Spinous layer (eg; *Hailey-Hailey* disease, spongiotic dermatitis, friction blister etc) or suprabasal (eg; pemphigus vulgaris and pemphigus vegetans, paraneoplastic pemphigus, IgA pemphigus etc).

C. Subepidermal; which includes basal keratinocyte vacoulisation or lysis (eg; epidermolysis bullosa simplex, erythema multiforme, *Stevens-Johnson* syndrome/ toxic epidermal necrolysis, fixed drug eruption etc) and basement membrane damage(eg; bullous pemphigoid, dermatitis herpetiformis, linear IgA disease, dystrophic epidermolysis bullosa, bullous lupus erythematosus etc.) [**14**].

2. Classification on the basis of mechanism of blister formation: The blister formation can occur as a result of spongiosis (eg; spongiotic dermatitis), acantholytic (eg; pemphigus group of diseases), ballooning degeneration (eg; viral infections especially herpes group); cytolytic (eg; erythema multiforme), or basement membrane damage (eg; bullous pemphigoid, dermatitis herpetiformis, linear IgA disease etc.) [**15**].

3. Classification based on the type of inflammatory infiltrate: Bullous disorders can be classified according to the predominant cell type present in the infiltrate as given under:

-Eosinophils: Bullous pemphigoid, pemphigoid gestationis.

-Lymphocytes: Spongiotic dermatitis, erythema multiforme.

-Neutrophils: Dermatitis herpetiformis, linear IgA disease, IgA pemphigus, bullous lupus erythematosus.

-Neutrophils and eosinophils: Epidermolysis bullosa acquisita, cicatricial pemphigoid [**16**].

4. Classication of bullous disorders according to whether they are autoimmune or not.

1. Immune-mediated bullous disorders eg; Pemphigus and its variants, bullous pemphigoid, mucous membrane pemphigoid, linear IgA disease, epidermolysis bullosa acquisita, pemphigoid gestationis, dermatitis herpetiformis etc.

2. Bullous disorders without associated autoantibodies eg; epidermolysis bullosa, porphyrias, erythema multiforme, staphylococcal scalded skin syndrome, *Grover*'s disease [**17**].

5. Classification of bullous disorders according to the morphology of lesions viz.

Flaccid bullae (pemphigus and its variants), tense bullae (eg; bullous pemphigoid), flaccid blisters and erosions (pemphigus vulgaris), superficial crusts (pemphigus foliaceus), vegetating lesions (pemphigus vegetans), polymorphous lesions (paraneoplastic pemphigus) and vesicles and pustules

(dermatitis herpetiformis, viral infections, miliaria etc.) [**18**].

Clinical Features

The blistering disorders present with the eruption of vesicles and bullae on normal or erythematous skin which can be localised or generalised. Itching may be present, and may precede the development of a fresh crop of blisters. The blisters may be flaccid or tense. The blisters may rupture to leave behind painful areas of oozing and denuded skin that may continue to expand. The most common subtype i.e; pemphigus vulgaris presents with oral blisters and erosions in 50-70% of patients, often resulting in a delay in the diagnosis. The skin lesions may appear after a period of several weeks to a year or more [**19**].

These diseases may present with vesicles and pustules (eg; dermatitis herpetiformis), involvement of mucous membranes (oral, ocular, nasal, pharangeal, genital in paraneoplastic pemphigus. Besides consulting dermatologists, the patients may present to ophthalmologists, dentists, otorhinolaryngologists or gynaecologists because of the varied manifestations which make the blistering disorders a multispeciality problem. Hence appropriate diagnosis and management can significantly decrease the morbidity and mortality associated with these disorders [**20**].

Investigations

Following investigations need to be done in a case of blistering disorder.

Complete haemogram, urine examination (routine and microscopy), liver function tests, renal function tests, ECG, chest radiography, sputum examination and *Mantoux* test (if the patient is to be put on immunosuppressives), *Tzanck* smear (for acantholytic cells), skin biopsy (to see the level of cleavage, type of inflammatory infiltrate and mechanism of blister formation); Immunofluorescence (direct and indirect to determine the bound and circulating antibodies.

Specialised investigations which can done to arrive at a diagnosis include ELISA, electron microscopy, immunoprecipatation, immunoblotting and molecular genetic analysis.

Differential Diagnosis

The early oral lesions of pemphigus vulgaris may be confused with aphthous ulcers, erythema multiforme, primary herpetic gingivostomatitis, oral candidiasis and erosive lichen planus.

Pemphigus foliaceus may resemble seborrheic dermatitis.

Pemphigus erythematosus may have to be differentiated from seborrheic dermatitis or lupus erythematosus. Bullous pemohigoid may have to differentiated from epidermolysis bullosa acquisita and other subepidermal immunobullous diseases like linear IgA disease and dermatitis herpetiformis).

Treatment

The management of blistering disorders requires a multidisciplinary approach with involvement of dermatologists, internists, ophthalmologists, dentists, and otorhinolaryngologists. The treatment of blistering disorders can be generalised as under:

1. Assess the general condition, extent and severity of the disease.

2. Particular attention should be paid to general nursing care, nutrition and control of secondary infection.

3. Adequate nutrition may require oral supplementation with proteins and high calorie fluids. A soft, easily chewable diet is preferable in the presence of oral lesions. In case the patient is not able to take enough nutrition orally, a feeding tube or even parenteral nutrition may be needed. In severe cases, a venous cutdown may be needed to give fluids and drugs by the intravenous route. All these

contribute immeasurably in reducing morbidity and mortality in patients with severe disease.

4. Topical bland ointments, proper and regular dressings of the raw areas should be done until re-epithelisation takes place.

5. Antibiotics should be given, preferably following a culture and sensitivity report, since infection remains the bugbear for treatment.

6. Topical steroids, topical tacrolimus, intralesional steroids for given for localised and limited disease.

7. Patients with painful oral ulcers can be encouraged to mix hydrogen peroxide with warm water (1:1) and swish and spit out 4 times a day to remove necrotic tissue. Triamcinolone acetonide oral paste can be applied to a small piece of gauze and kept on the affected area for 10 minutes 3 times daily. Intralesional triamcinolone acetonide is helpful for intractable oral ulcers. Oral candidiasis should be treated with clotrimazole troches four times a day or with oral fluconazole 150-200mg 1-7 times per week.

8. Systemic steroids. These are the mainstay for the treatment of moderate to severe disease.

The other treatment modalities which are tried with variable results include:

-Pulsed therapy with mega-doses of steroids.

-Antimetabolites like azathioprine, cyclophosphamide, mycophenolate mofetil are used as steroid sparing agents.

-Dexamethasone-cyclophosphamide pulse therapy for pemphigus vulgaris.

-Tetracycline and nicotinamide combination.

-Dapsone.

-Gold.

-Plasmapheresis.

-Intravenous immunoglobulin G.

-Monoclonal antibodies like rituximab.

-Immunoadsorption for the adsorption of pathogenic antibodies [**21, 22**].

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